Amendments to the Specification

Please delete the paragraph at page 2, line 12 to page 3, line 3 and replace it with the following paragraph in which amendments have been indicated:

Although many converging lines of evidence support the "protein only" hypothesis for prion propagation[1], the existence of multiple distinct isolates or "strains" of agent which can be stably passed in inbred mice of the same prion protein genotype has yet to be satisfactorily explained within this model. Strains can be distinguished by their different incubation periods and patterns of neuropathology when passaged in mice[11]. A number of distinct strains of natural sheep scrapie are ~~recognised~~recognized, for instance, while BSE appears to be caused by a single strain of agent[9]. Support for the contention that strain specificity is encoded by PrP alone is provided by study of two distinct strains of transmissible mink encephalopathy prions which can be serially propagated in hamsters, designated hyper (HY) and drowsy (DY)[12]. The strains can be distinguished by differing physicochemical~~physiochemical~~ properties of the accumulated PrP^{Sc} in the brains of affected hamsters[13]. Following limited proteolysis, strain specific migration patterns of PrP^{Sc} on polyacrylamide gels can be seen. DY PrP^{Sc} appears to be more protease sensitive than HY PrP^{Sc}, producing a different banding pattern of PrP^{Sc} on Western blots following proteinase K treatment. This relates to different N-terminal ends of HY and DY PrP^{Sc} following protease treatment and implies differing conformations of HY and DY ~~PrP^{Sc14}~~ $PrP^{Sc\,14}$. Furthermore, the demonstration that these strain specific physicochemical~~physiochemical~~ properties can be maintained during *in vitro* production of protease resistant PrP, when PrP^{C} is mixed with HY or DY hamster PrP^{Sc}, further supports the concept that ~~prions~~prion strains involve different PrP conformers[15].

Please delete the paragraph at page 4, lines 9-12 and replace it with the following paragraph in which amendments have been indicated:

Comparing~~Comparison~~ and/or identifying similar physicochemical properties (unless including dissimilar physicochemical properties)~~physiochemical properties~~ are well known techniques in the art. Comparison of any physicochemical~~physiochemical~~ properties can be used, for example a comparison of protease resistance and/or glycoform ratios. A suitable protease resistance comparison is proteinase K resistance.

Please delete the paragraph at page 5, lines 9-11 and replace it with the following paragraph in which amendments have been indicated:

In the methods~~matters~~ according to the first aspect of the invention, the electrophoresis pattern of the known sample may have a pattern substantially similar to that of type 4 as shown in figure 4 or an equivalent ~~patent~~pattern when ~~electrophoresised~~electrophoresed under varied conditions.

Please delete the paragraph at page 6, lines 9-21 and replace it with the following paragraph in which amendments have been indicated:

A fourth aspect of the invention provides a method for assessing and/or predicting the susceptibility of an animal, in particular a human individual, to bovine spongiform encephalopathy or a derivative thereof, the method comprising the step of determining the genotype of the individual at polymorphic residue 129 of PrP. The determination may be whether the individual is homozygous or heterozygous at polymorphic residue 129 of PrP, in particular whether the animal is homozygous for methionine or valine at polymorphic residue 129 of PrP. The most susceptible genotype to bovine spongiform encephalopathy, to date, is homozygous for methionine (MM). This genotype appears in approximately 38% of the UK population. Other susceptible genotypes, in order of decreasing susceptibility are valine/valine homozygotes and methionine/valine heterozygotes. The method of the fourth aspect of the invention may be carried out

using DNA obtained from a biological sample of the animal, in particular where the biological sample is blood.

Please delete the paragraph at page 6, line 23 to page 7, line 2 and replace it with the following paragraph in which amendments have been indicated:

A fifth aspect of the invention relates to a kit for use in assessing and/or predicting the susceptibility of an animal, in particular a human individual, to bovine spongiform encephalopathy or a derivative thereof, which comprises at least one pair of primers suitable for PCR amplification of at least a portion of the gene coding for PrP. Suitable primers include

5'- GTTTTCCAGGCCCATCAGTG-3' (SEQ ID NO:1)
5'-CTATGCACTCATTCATTATGC-3' (SEQ ID NO:2)

Please delete the paragraph at page 15, lines 13-20 and replace it with the following paragraph in which amendments have been indicated:

The present invention describes ~~that~~ altered patterns of glycosylation that are involved in prion diseases and, in particular, distinguish bovine spongiform encephalopathy and new variant ~~Creudztfeldt-Jakob~~Creuztfeldt-Jakob disease from other forms of Creuztfeldt-Jakob disease. It is possible that particular glycosylated ~~form~~forms of PrP are involved in the production of, or the stability of, the disease related isoforms of PrP. Thus, inhibitors of the biosynthetic processing pathway for sugars attached to glycoproteins will inhibit prion replication and can therefore be used to form the basis of therapeutic agents for animal and human prion disease.

Please delete the paragraph at page 26, lines 4-14 and replace it with the following paragraph in which amendments have been indicated:

There ~~was~~were striking similarities in PrP deposition patterns between ~~BSE-and~~ BSE- and vCJD-inoculated animals (detailed neuropathological studies will be

published elsewhere). Such patterns are determined by host genotype as well as by agent strain. We saw distinct patterns in the two types of mice, but, in each case, vCJD and BSE produced closely similar patterns. In ~~vCJD and~~vCJD- and BSE-inoculated non transgenic mice, there were PrP plaques and diffuse PrP deposition. In ~~vCJD and~~vCJD- and BSE-inoculated HuPrP$^{+/+}$ *Prn-P*$^{0/0}$ transgenic mice we saw a predominantly pericellular pattern of PrP immunostaining (data not shown). PrP plaques are a rare feature of prion disease in mice. Occasional mock-inoculated transgenic mice showed weaker and less extensive pericellular PrP immunostaining, probably reflecting the high level of PrP^{C} overexpression in these mice. Western blotting for PrP^{Sc} was negative in all these controls.

Please delete the paragraph at page 26, lines 16-21 and replace it with the following paragraph in which amendments have been indicated:

We performed western blot analysis to determine the PrP^{Sc} types produced in these transmissions. We have previously shown that the PrP^{Sc} type seen in vCJD (type 4) has a ratio of glycoforms closely similar to that of BSE passaged in several other species[2]. vCJD-inoculated ~~FVC~~FVB mice produced mouse PrP^{Sc} with type 4-like glycoform ratios and fragment sizes indistinguishable from those in BSE-inoculated FVB mice (Fig. 1a,b).

Please delete the paragraph at page 26, lines 24-27 and replace it with the following paragraph in which amendments have been indicated:

In transmission of vCJD to HuPrP$^{+/+}$ *Prn-p*$^{0/0}$ transgenic mice, where human PrP^{Sc} is generated, fragment sizes in inoculum can be directly compared. Again the PrP^{Sc} produced had type 4-like glycoform ratios. However, the fragment sizes differ from those in the inoculum and were indistinguishable from those in the type-2 PrP^{Sc} pattern (Fig. 1c). We have designated this new ~~patter~~pattern type 5.

Please delete the paragraph at page 27, lines 13-22 and replace it with the following paragraph in which amendments have been indicated:

The prion titres in these primary inocula are unknown but may be higher in the human cases, because cattle with BSE will have been culled before the terminal stages of disease. However, on clinical, pathological and molecular criteria, vCJD shows remarkable similarity in its transmission characteristics to BSE, and is quite distinct from all other forms of sporadic and acquired CJD. These data provide compelling evidence that BSE and vCJD are caused by the same prion strain. Taken together with the temporal and spatial ~~assication~~association of vCJD with BSE but not with scrapie or other animal prion diseases, and BSE transmission studies in macaques, this strongly suggests that vCJD is caused by BSE exposure. The theoretical possibility that both BSE and vCJD arise from exposure to a common unidentified source appears remote.

Please delete the paragraph at page 27, lines 24-27 and replace it with the following paragraph in which amendments have been indicated:

The production of a distinct molecular strain type on transmission of vCJD to mice expressing valine 129 human PrP suggests that BSE transmitted to humans of this genotype might produce a similar strain. Such cases may differ in their clinical and pathological phenotype to vCJD, but could be identified by PrP^{Sc} typing.

Please delete the paragraph at page 30, lines 18-19 and replace it with the following paragraph in which amendments have been indicated:

23. Parchi, P., Castellani, R., Capellari, S., et al. *Annals of Neurology* **39**, ~~669-680~~767-778 (1996).

Please insert the enclosed sequence listing after the last page (page 31) of the specification before the claims.